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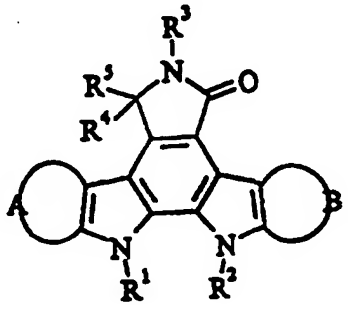
(54) Title: COMPOUNDS FOR THE TREATMENT OF RESTENOSIS

(57) Abstract

The present invention is concerned with compounds of formula (I) having use in the prophylaxis or treatment of restenosis. In particular, the invention relates to the use of these compounds in the manufacture of medicaments for the prophylaxis or treatment of restenosis, to medicaments obtained thereby, and to a method for treatment to prevent or alleviate restenosis using the compounds of the invention or a medicament containing said compounds.



(I)

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US	United States of America
UZ	Uzbekistan
VN	Viet Nam

COMPOUNDS FOR THE TREATMENT OF RESTENOSIS

The present invention is concerned with compounds having use in the prophylaxis or treatment of restenosis. In particular, the invention relates to the use of these compounds in the manufacture of medicaments for the prophylaxis or treatment of restenosis, to medicaments obtained thereby, and to a method for treatment to prevent or alleviate restenosis using the compounds of the invention or a medicament containing said compounds.

Restenosis can occur following a number of surgical techniques, for example, transplant surgery, vein grafting, coronary by-pass grafting and, most commonly, following angioplasty.

Angioplasty is a surgical technique wherein atherosclerotic stenoses in the peripheral, renal and coronary vasculature are opened up by compressing and/or tearing the plaque on the vessel walls, typically by means of a pressurised balloon catheter. Unfortunately, in 25 to 50 % of cases, particularly those involving the coronary vasculature, the treated vessel restenoses within a few months so that the operation must be repeated. Alternatives to the balloon catheter, such as pulsed lasers and rotary cutters, have been developed with a view to reducing or preventing restenosis following angioplasty, but have met with limited success. A number of drugs including anti-coagulants and vasodilators have also been tried with disappointing or equivocal results.

There is now a strong body of evidence, from work done both *in vitro* and *in vivo*, indicating that restenosis is a multifactorial process. Several cytokines and growth factors, acting in concert, stimulate the migration and proliferation of vascular smooth muscle cells (SMC) and production of extracellular matrix material, which accumulate to occlude the blood vessel. One growth factor in particular, platelet-derived growth factor (PDGF), is a potent mediator of SMC proliferation and migration.

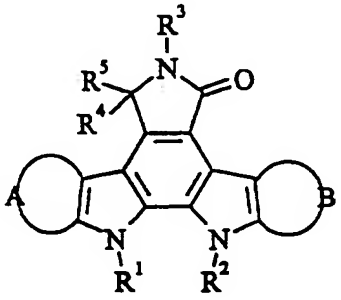
Several observations place PDGF in a central role in the restenosis process and suggest that an inhibitor of PDGF action would be therapeutically useful. One approach to blocking PDGF action is to inhibit at the level of the PDGF receptor. It is now clearly established that the intrinsic tyrosine kinase activity of the PDGF receptor is absolutely required for PDGF-dependent SMC proliferation and migration. Therefore, inhibiting

PDGF receptor tyrosine kinase activity would be expected to block the biological effects of PDGF and reduce the extent of restenosis.

We have now identified a class of compounds which are inhibitors of the platelet-derived growth factor receptor (PDGFr) tyrosine kinase.

Patent applications WO 93/18766 and WO 95/07910 disclose indole derivatives and their use in medical therapy. It is these compounds which we have now found to be useful in the prophylaxis or treatment of restenosis.

According to the present invention, there is provided use of compounds of formula (I)



(I)

wherein:

R^1 and R^2 are independently selected from:

-H,

$-OR^6$, $-COR^6$, $-CO_2R^6$,

where R^6 is C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl (for example phenyl), arylalkyl (for example benzyl), C_{2-6} alkenyl, or H,

$-NR^7R^8$

where R^7 and R^8 are independently selected from H, $-COR^6$ (where R^6 is as defined above), C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, and arylalkyl, or R^7 and R^8 together with the N atom to which they are attached form a 3-, 4-, 5- or 6-membered heterocyclic ring (for example piperidine, pyrrolidine) in which from

1 to 3 of the carbon atoms are replaced by heteroatoms independently selected from O, N and S (for example, morpholino, piperazine) which ring may where possible be partially or completely unsaturated, and

-C_{1-4}alkyl, C_{2-4}alkenyl, C_{3-8}cycloalkyl,
where the alkyl, alkenyl or cycloalkyl moiety may be optionally substituted by one or more substituents selected from:
halogen, cyano, nitro, azido,
-OR^6, -SR^6, -SO_2R^6 (where R^6 is as defined above),
-NR^7R^8, -T-C(Z)-NR^7R^8 (where T is NH or S, Z is NH, S or O and $R^7$and R^8 are as defined above),
heterocycle, -NH-heterocycle, heteroaryl, and aryl (for example phenyl, pyridyl, furyl, thienyl, pyrrole, naphthyl) optionally substituted by one or more substituents selected from -OR^6, -NR^7R^8, -SR^6, -SO_2R^6, -CO_2R^6, nitro, cyano, SCN, C_{1-6}alkyl, C_{3-6}cycloalkyl, haloalkyl (for example trifluoromethyl), hydroxylalkyl, -$CONH_2$, halogen and methylenedioxy, (where R^6,R^7, and R^8 are each as defined above);

R^3 is selected from:

-H,

-COR^6, -CH_2OR^6, -CO_2R^6, -OR^6 (where R^6 is as defined above),

-NR^7R^8, and -$CH_2NR^7R^8$ (where R^7 and R^8 are as defined above);

R^4 and R^5 either together with the carbon atom to which they are attached form a carbonyl group (>=O) or R^4 is H and R^5 is selected from H, -OR^6,and -SR^6, (where R^6 is as defined above);

A and B, which may be the same or different, together with the carbon atoms to which they are attached each represent a phenyl ring in which from 1 to 3 carbon atom(s) may be replaced by nitrogen atom(s), the nitrogen atom(s) being optionally substituted with an oxide group;

A and B are optionally substituted by one or more ring substituent(s) selected from:

-C_{1-6}alkyl optionally substituted by -OR^6 (where R^6 is as defined above), halogen (for example trifluoromethyl), or -NR^7R^8 (where R^7 and R^8 are as defined above),

cyano, nitro, halogen, methylenedioxy,

-OR^6, -SR^6, -SOR^6, -SO_2R^6, -CO_2R^6, -NHCOR^6
(where R^6 is as defined above),

-$SO_2NR^7R^8$, -$NHSO_2R^8$, -$CONR^7R^8$, and -NR^7R^8
(where R^7 and R^8 are as defined above);

provided that when A and B together with the carbon atoms to which they are attached both represent a phenyl ring R^3 is not -CH_2OR^6 or -$CH_2NR^7R^8$ and rings A and B are not substituted by -NHCOR^6, (where R^6, R^7, and R^8 are as defined above);

or a physiologically functional derivative thereof or a solvate of any thereof for use in the manufacture of a medicament for the treatment or prophylaxis of restenosis.

Preferred compounds of formula (I) are as defined above wherein R^3 is hydrogen and R^4 and R^5 together with the carbon atom to which they are attached form a carbonyl group; or a physiologically functional derivative thereof or a solvate of any thereof.

Further preferred compounds of formula (I) are as defined above wherein ring A and B together with the carbon atoms to which they are attached both represent a phenyl ring or one of A and B represents a phenyl ring and the other represents a pyridyl ring fused at the 2- and 3- positions; or a physiologically functional derivative thereof or a solvate of any thereof.

Preferred compounds of formula (I) include:

(i) 12-(2,3-Dihydroxy-1-propyl)-12,13-dihydro-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione;

(ii) 12,13-Dihydro-3,9-dimethoxy-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione;

(iii) 12,13-Dihydro-3,9-dihydroxy-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione;

(iv) 13-Ethyl-12,13-dihydro-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione;

(v) 12-(3-Aminopropyl)-12,13-dihydro-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione;

(vi) 13H-12-Ethylpyrido[2',3':2,3]pyrrolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione;

(vii) 12,13-Dihydro-pyrido[2',3':2,3]pyrrolo[3,4-c]carbazole-5,7(6H)-dione; and

(viii) 12-(3-Propanamide)-12,13-dihydro-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione;

and physiologically functional derivatives thereof and solvates of any thereof.

Certain compounds of formula (I) as defined above are new compounds and represent a further feature of the present invention collectively as compounds of formula (IA) wherein:

R^1 is H and R^2 is:

$-C_{2-4}$alkyl
optionally substituted by one or more substituents selected from:
$-OR^{6'}$, halogen, cyano, and $-NR^{7'}R^{8'}$,
where $R^{6'}$ is C_{1-4}alkyl, C_{2-6}alkenyl, or H,
where $R^{7'}$ is H and $R^{8'}$ is C_{1-4}alkyl;

R^3 is H;

R^4 and R^5 together with the carbon atom to which they are attached form a carbonyl group (>=O);

A and B together with the carbon atoms to which they are attached each represent a phenyl ring optionally substituted by one or more ring substituent(s) selected from:

$-OR^{6'}$, $-CO_2R^{6'}$ (where $R^{6'}$ is as defined above),
cyano, nitro,
$-C_{1-4}$alkyl optionally substituted with $-OR^{6'}$ (where $R^{6'}$ is as defined above), and
$-NR^{7''}R^{8''}$
where $R^{7''}$ and $R^{8''}$ are independently selected from H and C_{1-4}alkyl;

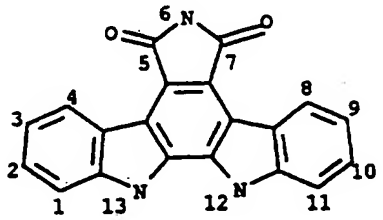
provided that when A and B are both unsubstituted phenyl rings R^2 is not ethyl or 2,3-dihydroxypropyl;

or a physiologically functional derivative thereof or a solvate of any thereof.

Preferred compounds of formula (IA) are as defined above where at least one of the phenyl rings A and B is substituted by one or more substituents as defined above.

Further preferred compounds of formula (IA) are as defined above where ring A is substituted at either position 2 or 3, or both, and/or ring B is substituted at either position 9 or 10, or both.

The exact position of substituents on ring A and B defined above can be determined by reference to the illustrative structure given below.



Preferred compounds of formula (IA) include:

(i) 12-Ethyl-12,13-dihydro-10-amino-5H-indolo[2,3a]pyrrolo[3,4c]carbazole-5,7(6H)-dione;

(ii) 12-Ethyl-12,13-dihydro-10-carboxy-5H-indolo[2,3a]pyrrolo[3,4c]carbazole-5,7(6H)-dione;

(iii) 12-Propyl-12,13-dihydro-5H-indolo[2,3a]pyrrolo[3,4c]carbazole-5,7(6H)-dione;

(iv) 12-(2,2,2-Trifluoroethyl)-12,13-dihydro-5H-indolo[2,3a]pyrrolo[3,4c] carbazole-5,7(6H)-dione;

(v) 12-(3-Hydroxypropyl)-12,13-dihydro-5H-indolo[2,3a]pyrrolo[3,4c] carbazole-5,7(6H)-dione;

(vi) 12-(2,3-Dihydroxybutyl)-12,13-dihydro-5H-indolo[2,3a]pyrrolo[3,4c] carbazole-5,7(6H)-dione; and

(vii) 12-(13-Acetoxypropyl)12,13-dihydro-5H-indolo[2,3a]pyrrolo[3,4c]carbazole-5,7(6H)-dione;

and physiologically functional derivatives thereof and solvates of any thereof.

Further features of the invention include:

(i) A compound of formula (IA) or a physiologically functional derivative thereof or a solvate of any thereof for use in the treatment or prophylaxis of restenosis.

(ii) The use of compounds of formula (IA) or a physiologically functional derivative thereof or a solvate of any thereof in the manufacture of a medicament for the prevention or treatment of restenosis.

As used herein, the term "alkyl" as a group or part of a group means a straight or

branched chain alkyl group. Such alkyl groups preferably have from 1 to 3 carbon atoms. As used herein, the term "aryl" as a group or part of a group includes phenyl, pyridyl, naphthyl, pyrrolo, thienyl, furyl, the term heteroaryl includes a 5- or 6-membered ring where from 1 to 3 atom(s) are selected from N, O, and S, optionally fused to an aryl ring (for example quinolyl, isoquinolyl, benzimidazolyl, benzotriazolyl, benzothienyl, benzoxazolyl, benzothiazolyl, etc.), and the term heterocycle includes a 5- or 6- membered ring where from 1 to 3 carbon atom(s) are replaced by atom(s) selected from N, O, and S (for example morpholine, pyrrolidine, piperidine, piperazine) which may be partially or completely saturated.

Preferred esters in accordance with the invention include carboxylic acid esters in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, methyl, n-propyl, t-butyl, or n-butyl), cycloalkyl, alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted by, for example, halogen, C_{1-4} alkyl, or C_{1-4} alkoxy), or amino; sulphonate esters, such as alkyl- or aralkylsulphonyl (for example, methanesulphonyl); amino acid esters (for example, L-valyl or L-isoleucyl); and mono-, di-, or tri-phosphate esters. In such esters, unless otherwise specified, any alkyl moiety present advantageously contains from 1 to 18 carbon atoms, particularly from 1 to 6 carbon atoms, more particularly from 1 to 4 carbon atoms. Any cycloalkyl moiety present in such esters advantageously contains from 3 to 6 carbon atoms. Any aryl moiety present in such esters advantageously comprises a phenyl group. Any reference to any of the above compounds also includes a reference to a pharmaceutically acceptable salt thereof and to a solvate of any thereof.

Examples of pharmaceutically acceptable salts of the compounds of formula (I) and physiologically functional derivatives thereof include salts derived from an appropriate base, such as an alkali metal (for example, sodium), an alkaline earth (for example, magnesium), ammonium and NX_4^+ (wherein X is C_{1-4}alkyl); salts derived from an appropriate acid, for example, organic carboxylic acids such as acetic, lactic, tartaric, malic, isethionic, lactobionic and succinic acids, organic sulphonic acids, such as methanesulphonic, ethanesulphonic, benzenesulphonic and p-toluenesulphonic acids, and inorganic acids, such as hydrochloric, sulphuric, phosphoric and sulphamic acids.

As used herein, the term "physiologically functional derivative" means a chemical derivative, for example a physiologically acceptable salt, ester, or salt of such ester, of a compound of formula (I) or (IA) which has the same physiological function as the free compound of formula (I) or (IA), for example, by being convertible in the body to the free compound of formula (I) or (IA) or an active metabolite or residue thereof.

The present invention further includes a method for the treatment of a mammal, such as a human, to prevent or alleviate restenosis, for example, restenosis following angioplasty which comprises the administration of a therapeutically effective amount of a compound of formula (I) or (IA) or a physiologically functional derivative thereof or a solvate of any thereof.

For brevity, the term "a compound of the invention" is used hereinafter to describe a compound of formula (I) or (IA) or any of its physiologically functional derivatives, or solvates of any thereof.

The amount of a compound of the invention required to achieve a therapeutic effect will, of course, vary with the specific compound chosen, the route of administration, the subject under treatment, and the particular condition which is to be prevented. A suitable daily dose for a mammal is in the range 0.5 to 120mg of compound/kilogram bodyweight, the preferred daily dosage being 2 to 60mg/kg, which may be administered as two or more sub-doses daily.

While it is possible for a compound of the invention to be administered alone, it is preferable to present it as a pharmaceutical formulation comprising the compound of the invention in association with a pharmaceutically acceptable carrier or excipient and, optionally, one or more other therapeutic ingredients. The present invention, therefore, also provides pharmaceutical formulations for use in the prophylaxis or treatment of restenosis, for example, restenosis following angioplasty containing a compound of formula (I) or (IA) or a physiologically functional derivative thereof or a solvate of any thereof, at least one pharmaceutical carrier or excipient and, optionally, one or more other therapeutic ingredients.

The pharmaceutical carrier or excipient must, of course, be compatible with the other ingredients in the formulation and must not be detrimental to the patient. The active

ingredient may comprise from 0.1% to 99.9% by weight of the formulation. Typical unit doses of a pharmaceutical formulation according to the invention contain from 1 to 1500mg and preferably from 10 to 700mg of the active ingredient.

Pharmaceutical formulations according to the invention may be adapted for administration by oral or parenteral (including intravenous, intradermal or intramuscular) routes, or may also be administered during the surgical procedure *via* an angioplasty cannula (for example, a 1-50mg dose); by this means the formulated drug is introduced at the site of the angioplasty through perforations in the balloon catheter used to open up the atherosclerotic stenosis. In a further mode of administration, the resulting restenosis may be 'held open' by means of a tubular stent which may be impregnated with a compound of the invention which gradually leaches into the site of the angioplasty.

Pharmaceutical formulations of the invention may conveniently be presented in unit dosage form and may be prepared by any method known in the art of pharmacy. Such methods include the step of bringing the active ingredient into association with a carrier or excipient and, optionally, containing one or more accessory ingredients. In general, pharmaceutical formulations are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier, or both, and then, if desired, shaping the product into the required form.

Pharmaceutical formulations adapted for oral administration may be in the form of discrete units such as capsules, cachets, tablets, or lozenges, each containing a predetermined amount of the active ingredient; in the form of a powder or granules; in the form of a solution or suspension in an aqueous or non-aqueous liquid; edible foams or whips; or in the form of an oil-in-water or water-in-oil emulsion. The formulation may also be in the form of a bolus, electuary, or paste.

A tablet may be made by compressing or moulding the active ingredient, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form, such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent and/or surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered active ingredient and a suitable carrier or

excipient moistened with an inert liquid diluent.

Pharmaceutical formulations adapted for parenteral administration typically comprise a sterile aqueous or non-aqueous preparation of the active ingredient (where necessary, solubilised in a small amount of an appropriate organic solvent) which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the patient. Such formulations may also be in the form of aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example, water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets.

Pharmaceutical formulations suitable for administration *via* an angioplasty cannula are typically the same as those used for intravenous administration.

In addition to the aforementioned ingredients, the formulations may include one or more additional ingredients conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

The compounds of the invention may be prepared by one or more of the methods described in WO 93/18766, WO 93/24491, and pending WO 95/07910 which are incorporated herein by reference.

Example 1

Preparation of 3-(1-(n-propyl)-1H-indol-3-yl)-4-(1H-indol-3-yl)-1-methyl-2,5-dihydro-1H-pyrrolo-2,5-dione

To a solution of 3,4-bis-(1H-indol-3-yl)-1-methyl-2,5-dihydro-1-H-pyrrolo-2,5-dione (2.14g, 6.27mmol) in DMF (30ml) was added NaH (80%, 280mg). After 20 minutes at room temperature, propyl iodide (0.7ml) was added and the mixture stirred overnight at room temperature. The mixture was quenched by the addition of acetic acid (2ml),

evaporated in vacuo and chromatographed over flash silica, eluting with hexane/ethyl acetate (3:1), (2:1) and (1:1). Pooling and evaporation of the appropriate fractions afforded the title compound as a red solid.
M.p. 159-160°C

The following compound was prepared by a similar method, replacing propyl iodide with 2-iodo-1,1,1-trifluoroethane.

Example 1A

3-(1-(2,2,2-Trifluoroethyl)-1H-indol-3-yl)-4-(1H-indol-3-yl)-1-methyl-2,5-dihydro-1H-pyrrolo-2,5-dione

M.p. 247°C

Example 2

3-(1-Ethyl-6-cyano-1H-indol-3-yl)-4-(1H-indol-3-yl)-1H-pyrrolo-2,5-dione

Triethyloxonium tetrafluroborate (3.99g) was added to a suspension of indole-3-acetamide (3.48g, 20mmol) in dichloromethane (100ml) and the mixture warmed gently to effect dissolution. After stirring for 2 hours at room temperature, ethyldiisopropylamine (14ml) was added (solution A).

To a solution of 6-cyano-1-ethylindole (3.4g 20mmol) in dry dichloromethane (50ml) was added oxalyl chloride (1.74ml) and the solution stirred at room temperature for 3 hours. After evaporation of the solvent in vacuo, and co-evaporation with dry dichloromethane, the material was suspended in dry dichloromethane (100ml) and added dropwise to solution A at room temperature and stirred for 24 hours.

Aqueous 10% sodium bicarbonate solution (80ml) was added, the organic layer separated, dried (Na_2SO_4) and evaporated until all of the solvent had been removed. The resulting orange foam was taken up in a mixture of dichloromethane (70ml) and toluene (35ml), and p-toluenesulphonic acid monohydrate (4.2g) added. After stirring overnight at room temperature, the red mixture was washed with 10% sodium

bicarbonate solution, separated, dried (Na_2SO_4) and evaporated. Purification by flash chromatography over silica, eluting with hexane/ethyl acetate (3:1), (2:1) and (1:1), followed by recrystallisation from ethyl acetate (1:1), gave the title compound as red crystals.

M.p. 183-184°C

Example 3

General Method for the Preparation of 3,4-Bis-(1H-indol-3-yl) maleic anhydrides

A solution of the 3,4-bis(1-H-indol-3-yl)-2,5-dihydro-1-methyl-1H-pyrrolo-2,5-dione in 10% aqueous potassium hydroxide and a co-solvent, preferably dioxane or methanol, was heated under reflux for 1-30 hours. When TLC analysis (SiO_2) revealed the absence of starting material, the mixture was cooled and acidified. If the product precipitated at this stage, it could be isolated by filtration and optionally crystallised. Alternatively, the product could be extracted, for example with ethyl acetate, and then purified by crystallisation or column chromatography over silica. Often the product could be used directly in the next step without purification.

The following examples where thus prepared.

Example 3A

3-(1H-Indol-3-yl)-4-(1-(2,2,2-trifluoromethyl)-1H-indol-3-yl)maleic anhydride

After acidification, extraction and evaporation, this was used directly in the next step.

Example 3B

3-(1H-Indol-3-yl)-4-(1-(n-propyl)-1H-indol-3-yl)maleic anhydride

After acidification, extraction and evaporation, this was used directly in the next step.

Example 4

Preparation of 3-(1-Ethyl-6-nitro-1H-indol-3-yl)-4-(1-(p-toluene sulphonyl)-1H-indol-3-yl)maleic anhydride

To a solution of 1-ethyl-6-nitroindole (2.3g, 12mmol) in dry dichloromethane (50ml) was added oxalyl chloride (3ml, 3eq) and the solution stirred at room temperature for 3 hours. The solvent was removed in vacuo, co-evaporated with dry dichloromethane, and suspended in dry dichloromethane (120ml). This was added slowly to a mixture of 1-p-toluene sulphonyl indole 3-acetic acid (4g, 12mmol) and ethyldiisopropylamine (2.2ml, 2eq) in dichloromethane (30ml) and the mixture stirred overnight at room temperature. A further 1.1ml ethyl diisopropylamine was added and the mixture stirred for a further 2 days. The mixture was washed with aqueous sodium bicarbonate solution (10%), the organic layer separated, dried (Na_2SO_4) and evaporated. Chromatography over flash silica eluting with hexane/ethyl acetate (10:1), then (4:1), 2:1), (1:1) and finally (1:2) gave the product as a bright yellow solid.

Example 5

Preparation of 3-(1-Ethyl-6-nitro-1H-indol-3-yl)-4-(1H-indol-3-yl)maleic anhydride

Example 2 (2.3g) in methanolic potassium hydroxide solution (0.1M, 400ml) was heated under reflux for 9.5 hours. The methanol was evaporated in vacuo, HCl (2N, 200ml) added to give a solution of pH 1-2, the mixture extracted with ethyl acetate (300ml), the organic layer separated, washed with brine and dried (Na_2SO_4). Evaporation afforded the product as a red solid.

Example 6

General Method for the Preparation of 3,4-bis-(1H-indol-3-yl)-2,5-dihydro-1H-pyrrolo-2,5-diones from 3,4-bis (1H-indol-3-yl) maleic anhydrides

A mixture of the 3,4-bis(1H-indole-3-yl) maleic anhydride and an excess of ammonium acetate (typically 10-250 equivalents) were heated at 140°C until reaction was complete (typically 15-240 minutes). The mixture was then cooled, partitioned between ethyl

acetate and water (brine, aqueous HCl or bicarbonate solution may be used), and the organic phase separated. After further washings, the organic phase is dried ($MgSO_4$) and evaporated. The product may then be recrystallised or purified by flash chromatography over silica. The following examples were thus prepared.

Example 6A

3-(1H-Indol-3-yl)-4-(1-(2,2,2-trifluoromethyl)-1H-indol-3-yl)-2,5-dihydro-1H-pyrrolo-2,5-dione

M.p. 238°C

Example 6B

3-(1H-Indol-3-yl)-4-(1-(n-propyl)-1H-indol-3-yl)-2,5-dihydro-1H-pyrrolo-2,5-dione

M.p. 172-173°C

Example 6C

3-(1-Ethyl-6-nitro-1H-indol-3-yl)-4-(1H-indol-3-yl)-2,5-dihydro-1H-pyrrolo-2,5-dione

M.p. 272-273°C

Example 7

General methods for the preparation of 12,13-Dihydro-5H-indolo[2,3a]-pyrrolo [3,4c]carbazole-5,7(6H)-diones

a) To a solution of the 3,4-Bis(1H-indol-3-yl)-2,5-dihydro-1H-pyrrolo-2,5-dione derivative in xylene, toluene, or dioxane, or combinations thereof at 100-140°C was added 2,3-dichloro-5,6-dicyanobenxoquinone (1.1 equivalents) and p-toluenesulphonic acid (0.01-1.2 equivalents). The mixture was maintained at this temperature until TLC monitoring indicated that the reaction was complete

(usually 1-60 minutes). The mixture was then cooled. If the product precipitated, it was isolated by filtration and recrystallisation. Otherwise sodium bicarbonate solution was added and the organic layer separated, dried (Na_2SO_4) and evaporated. Some examples can be purified by recrystallisation at this stage. Otherwise the products were purified by flash chromatography over silica or basic alumina (eluted with hexane, ethyl acetate, acetone, THF, or combinations thereof).

b) A solution of the 3,4-bis(1H-indol-3-yl)-2,5-dihydro-1H-pyrrolo-2,5-dione in a suitable solvent (preferably isopropanol) containing iodine (1.2eq) was irradiated (λ, 254-350nM) for 1-7 days whilst oxygen or preferably nitrogen was bubbled through the solution. If the product precipitated it was isolated by filtration and crystallised from a suitable solvent (ethyl acetate, acetone, DMF, DMSO). If not, the solvent was evaporated in vacuo, the residue taken up in ethyl acetate and washed successively with sodium thiosulphate solution and sodium bicarbonate solution, separated, dried (Na_2SO_4), evaporated and the product purified by crystallisation or flash chromatography over silica. The following compounds were thus prepared.

Example 7A

12-Ethyl-12,13-dihydro-10-cyano-5H-indolo[2,3a]pyrrolo[3,4c]carbazole-5,7(6H)-dione

M.p. >300°C

Example 7B

12-Propyl-12,13-dihydro-5H-indolo[2,3a]pyrrolo[3,4c]carbazole-5,7(6H)-dione

M.p. >335°C

Example 7C

12-(2,2,2-Trifluoroethyl)-12,13-dihydro-5H-indolo[2,3a]pyrrolo[3,4c]carbazole-5,7(6H)-dione

M.p. >330°C

Example 7D

12-Ethyl-12,13-dihydro-10-nitro-5H-indolo[2,3a]pyrrolo[3,4c]carbazole-5,7(6H)-dione

M.p. >300°C

Example 8

Preparation of 13-ethyl-12,13-dihydro-2-carboxy-5H-indolo[2,3a]pyrrolo[3,4c]-carbazole-5,7(6H)-dione

A mixture of 7A (118mg) in dioxan (20ml) and sodium hydroxide (20ml, 8N) was heated under reflux for 9 hours with vigorous stirring. Acidification with conc. HCl formed a yellow precipitate. Ethyl acetate (60ml), dioxan (30ml) and water (50ml) were added and the yellow-green organic layer separated. The aqueous layer was washed with ethyl acetate, the organic layers combined, dried (Na_2SO_4) and evaporated to dryness. The residue was taken up in DMF (10ml), HMDS (3ml) and methanol (3ml) were added and the solution stirred overnight at room temperature. Ethanol (2ml) was added and the solvent removed in vacuo. Recrystallisation from hexane/ethyl acetate gave the title compound as an orange solid.
M.p. >300°C.

Example 9

Preparation of 13-ethyl-12,13-dihydro-2-amino-5H-indolo[2,3a]pyrrolo[3,4c] carbazole-5,7(6H)-dione

A solution of (180mg) and 10% Pd/C (100mg) in DMF (100ml) was hydrogenated at 50 atmospheres for 18 hours. The mixture was filtered through hyfl , the filtrate

evaporated and chromatographed over flash silica, eluting with ethyl acetate containing 1% triethylamine. Pooling and evaporation of the appropriate fractions afforded the title compound as an orange solid, after recrystallisation from dimethyl sulphoxide.
M.p. >300°C

Example 10

Preparation of 12,13-Dihydro-3,9-dihydroxy-5H-indolo[2,3a]pyrrolo[3,4c]carbazole-5,7(6H)-dione

A mixture of 12,13-dihydro-3,9-dimethoxy-5H-indolo[2,3a]pyrrolo[3,4c]carbazole-5,7(6H)-dione (66mg) and pyridine hydrochloride (800mg) was heated to 180°C in a sealed tube and maintained at 180°C for one hour. Water and ethyl acetate were added, the organic layer washed with dilute HCl, then brine, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography over silica, eluting with hexane/ethyl acetate (4:1). Pooling and evaporation of the appropriate fractions afforded the product as an orange solid.
Mass spec (EI): 357 (M^+)
M.p. >300°C

Example 11

Preparation of 12-(3-Acetoxypropyl)12,13-dihydro-6-methyl-5H-indolo[2,3a]pyrrolo [3,4c]carbazole-5,7(6H)-dione

To a solution of 3,4-bis-(1H-indol-3-yl)-2,5-dihydro-1-methyl-1H-pyrrolo-2,5-dione (3.41g, 10mmol) in dry DMF (30ml) under nitrogen at 0°C was added NaH (60% in mineral oil, 440mg, 11mmol) and the mixture stirred at room temperature for 30 minutes. The mixture was cooled to -10°C and 3-chloropropylacetate (1.36g, 10mmol) added. The mixture was stirred overnight at room temperature, then evaporated to dryness, taken up in EtOAc and washed with brine. The organic fraction was dried (Na_2SO_4), evaporated and chromatographed over flash silica. Elution with hexane/EtOAc (5:2) gave 3-(1-(3-acetoxypropyl)-1H-indol-3-yl)-4-(1H-indol-3-yl)-2,5-dihydro-1-methyl-1H-pyrrolo-2,5-dione as a red solid.

Cycylisation was effected according to the method described in 7a), using toluene as the solvent. Chromatography over silica, eluting with hexane/EtOAc (1:1) gave the title compound (11) as a yellow-green powder.
M.p. 237-240°C

Example 12

Preparation of 12-(3-Hydroxypropyl)12,13-dihydro-5H-indolo[2,3a]pyrrolo [3,4c]carbazole-5,7(6H)-dione

A solution of 11 (509mg) in dioxan (40ml) and 10% KOH solution (100ml) was stirred at room temperature for 2 days. The mixture was neutralised with aqueous HCl and extracted with ethyl acetate. Chromatography over flash silica eluting with EtOAc/hexane (1:1), then (2:1), gave the cyclic anhydride. A mixture of the cyclic anhydride (387mg) and ammonium acetate (3.85g) was heated at 140°C for 2 hours. After cooling, the mixture was diluted with water and extracted twice with ethyl acetate. The combined organic extracts were dried ($MgSO_4$), evaporated and fractionated over flash silica, eluting with hexane/EtOAc (1:2) to give the title compound as a golden-yellow powder.
M.p. ~350°C (dec)

$C_{23}H_{17}N_3O_3.0.2CH_3CO_2Et$ requires C, 71.29%; H, 4.64%; N, 10.48%
Found C, 71.48%; H, 4.48%; N, 10.29%

Example 13

Preparation of 12-(2,3-Dihydroxybutyl)12,13-dihydro-5H-indolo[2,3a]pyrrolo [3,4c]carbazole-5,7(6H)-dione

To a suspension of 12,13-dihydro-6-methyl-5H-indolo[2,3a]pyrrolo[3,4c]carbazole-5,7(6H)-dione (204mg, 0.6mmol) in dry DMF (10ml) was added 60% NaH (28.8mg, 0.72mmol) under nitrogen and the mixture stirred at room temperature for 30 minutes. Crotyl chloride (58.5µL, 1eq) was added and the mixture stirred at room temperature overnight. The mixture was partitioned by the addition of aqueous HCl and EtOAc, the

organic layer separated, dried ($MgSO_4$), evaporated and chromatographed over flash silica. Elution with hexane/EtOAc (2:1), then (3:2), gave 12-(but-2-ene), 13-dihydro-6-methyl-5H-indolo[2,3a]pyrrolo[3,4c]carbazole-5,7(6H)-dione (13A).

A solution of 13A (118mg, 0.3mmol) in dioxan (5ml) and 10% KOH solution (5ml) was heated under reflux for 18 hours. The mixture was partitioned by the addition of aqueous HCl and EtOAc, the organic layer separated, dried ($MgSO_4$), evaporated and purified by flash chromatography over silica, eluting with hexane/EtOAc (2:1), (1:1), then EtOAc, affording the cyclic anhydride (13B).

A solution of 13B (49.4mg) in DMF (3ml), HMDS (273µL) and MeOH (25.7µL) was stirred overnight at room temperature. A further 140µL HMDS and 13µL MeOH was added and stirring continued for 2 days. Aqueous HCl was added, and the resulting precipitate filtered off. This was purified by flash chromatography over silica, eluting with hexane/EtOAc (2:1), (3:2), and finally (1:1), to afford 12-(but-2-ene), 13-dihydro-5H-indolo[2,3a]pyrrolo[3,4c]carbazole-5,7(6H)-dione (13C).

To a solution of 13C (30mg, 0.08mmol) in acetone (6ml) was added N-methyl morpholine N-oxide (23.1mg, 0.11mmol) followed by osmium tetroxide (1 crystal) and one drop of water. The mixture was stirred overnight at room temperature, diluted with acetone, absorbed onto flash silica and purified by flash chromatography over silica, eluting with EtOAc/hexane (3:1). This afforded the title compound (13) as a yellow powder.

M.p. 285-288°C

Anal. $C_{24}H_{19}N_3O_4.0.5H_2O$ requires C, 68.25%; H, 4.74%; H, 9.95%

Found C, 68.27%; H, 4.55%; N, 9.78%

PHARMACEUTICAL FORMULATION EXAMPLE

The "active ingredient" in the following formulation example is a compound of the invention as defined above.

Liposome dispersion

Ingredients		Quantity
Active ingredient		100mg
Dipalmitoyl phosphatidylcholine		25.1mg
Cholesterol		13.0mg
Phosphatidylserine		3.8mg
Sodium chloride		9.0mg
Water for injection	to make	1ml

BIOLOGICAL DATA

PDGFr Autophosphorylation Assay

Confluent monolayers of rat aortic smooth muscle cells (A10) were incubated in Dulbecco's Modified Eagles Media (DMEM) plus 0.2% foetal calf serum for 24hrs. After this period the cells were stimulated with PDGF in the presence or absence of inhibitor. The assay was terminated by harvesting the cells on ice in a lysis buffer. (5mM Tris pH8.0, 1% NP40, 150mM NaCl). The cell lysates were prepared for polyacrylamide gel electrophoresis by boiling with sodium dodecylsulphate (SDS) sample buffer (0.3125M Tris pH 6.8, 10% SDS, 50% glycerol 5mM dithiothreitol (DTT)) and separated using a discontinuous polyacrylamide gel electrophoresis system as described in Nature, 227, 680 (1970), Laemelli.

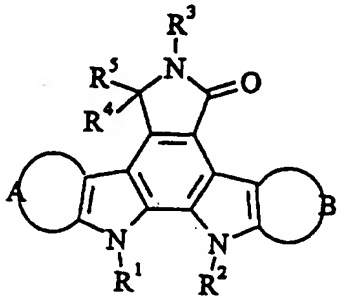
The separated phosphorylated proteins were transferred onto nitrocellulose membrane (Scheicher and Schuell. Anderman Kingston, Surrey) using an eletrophoretic Western blotting technique based on a method described in Anal. Biochem., 112, 195, (1981),Burnette.

The phosphotyrosine proteins were detected immunocytochemically using a mouse anti-phosphotyrosine monoclonal 4G10 (UBI Lake Placid, NY) followed by a second sheep anti-mouse IgG monoclonal with a radioiodinated label (Amersham Int., Little Chalfont, Bucks). The proteins were then visualised and quantitated using a PhosphoImager™ (Molecular Dynamics Sevenoaks, Kent).

When tested in this assay, representative compounds of the invention were found to significantly inhibit PDGFr tyrosine kinase at a concentration of 1μM. In particular, 12-(2,3-dihydroxy-1-propyl)-12,13-dihydro-5H-indolo[2,3-a]pyrrolo-[3,4-c]-carbazole-5,7(6H)dione and 12,13-dihydro-3,9-dimethoxy-5H-indolo[2,3-a]-pyrrolo[3,4-c]-carbazole-5,7(6H)dione were each found to have an IC_{50} of less than 50nM.

CLAIMS

1. Use of compounds of formula (I)



(I)

wherein:

R^1 and R^2 are independently selected from:

-H,

$-OR^6$, $-COR^6$, $-CO_2R^6$,
where R^6 is C_{1-6} alkyl, C_{3-7} cycloalkyl, aryl (for example phenyl), arylalkyl (for example benzyl), C_{2-6} alkenyl, or H,

$-NR^7R^8$
where R^7 and R^8 are independently selected from H, $-COR^6$ (where R^6 is as defined above), C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, and arylalkyl, or R^7 and R^8 together with the N atom to which they are attached form a 3-, 4-, 5- or 6-membered heterocyclic ring (for example piperidine, pyrrolidine) in which from 1 to 3 of the carbon atoms are replaced by heteroatoms independently selected from O, N and S (for example, morpholino, piperazine) which ring may where possible be partially or completely unsaturated, and

$-C_{1-4}$alkyl, C_{2-4}alkenyl, C_{3-8}cycloalkyl,
where the alkyl, alkenyl or cycloalkyl moiety may be optionally substituted by one or more substituents selected from:
halogen, cyano, nitro, azido,

$-OR^6$, $-SR^6$, $-SO_2R^6$ (where R^6 is as defined above),
$-NR^7R^8$, -T-C(Z)-NR^7R^8 (where T is NH or S, Z is NH, S or O and $R^7$and R^8 are as defined above),
heterocycle, -NH-heterocycle, heteroaryl, and aryl (for example phenyl, pyridyl, furyl, thienyl, pyrrole, naphthyl) optionally substituted by one or more substituents selected from $-OR^6$, $-NR^7R^8$, $-SR^6$, $-SO_2R^6$, $-CO_2R^6$, nitro, cyano, SCN, C_{1-6}alkyl, C_{3-6}cycloalkyl, haloalkyl (for example trifluoromethyl), hydroxylalkyl, $-CONH_2$, halogen and methylenedioxy, (where R^6,R^7, and R^8 are each as defined above);

R^3 is selected from:

-H,

$-COR^6$, $-CH_2OR^6$, $-CO_2R^6$, $-OR^6$ (where R^6 is as defined above),

$-NR^7R^8$, and $-CH_2NR^7R^8$ (where R^7 and R^8 are as defined above);

R^4 and R^5 either together with the carbon atom to which they are attached form a carbonyl group (>=O) or R^4 is H and R^5 is selected from H, $-OR^6$,and $-SR^6$, (where R^6 is as defined above);

A and B, which may be the same or different, together with the carbon atoms to which they are attached each represent a phenyl ring in which from 1 to 3 carbon atom(s) may be replaced by nitrogen atom(s), the nitrogen atom(s) being optionally substituted with an oxide group;

A and B are optionally substituted by one or more ring substituent(s) selected from:

$-C_{1-6}$alkyl optionally substituted by $-OR^6$ (where R^6 is as defined above), halogen (for example trifluoromethyl), or $-NR^7R^8$ (where R^7 and R^8 are as defined above),

cyano, nitro, halogen, methylenedioxy,

$-OR^6$, $-SR^6$, $-SOR^6$, $-SO_2R^6$, $-CO_2R^6$, $-NHCOR^6$
(where R^6 is as defined above),

$-SO_2NR^7R^8$, $-NHSO_2R^8$, $-CONR^7R^8$, and $-NR^7R^8$
(where R^7 and R^8 are as defined above);

provided that when A and B together with the carbon atoms to which they are attached both represent a phenyl ring R^3 is not $-CH_2OR^6$ or $-CH_2NR^7R^8$ and rings A and B are not substituted by $-NHCOR^6$, (where R^6, R^7, and R^8 are as defined above);

or a physiologically functional derivative thereof or a solvate of any thereof in the manufacture of a medicament for the treatment or prophylaxis of restenosis.

2. Use according to claim 1 of a compound of formula (I) selected from:

12-(2,3-Dihydroxy-1-propyl)-12,13-dihydro-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole -5,7(6H)-dione;

12,13-Dihydro-3,9-dimethoxy-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione;

12,13-Dihydro-3,9-dihydroxy-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione;

13-Ethyl-12,13-dihydro-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione;

12-(3-Aminopropyl)-12,13-dihydro-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione;

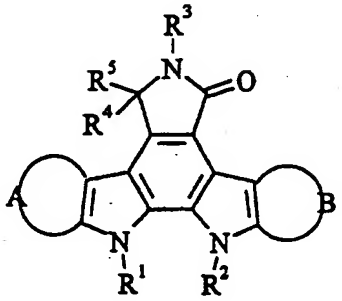
13H-12-Ethylpyrido[2',3':2,3]pyrrolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione;

12,13-Dihydro-pyrido[2',3':2,3]pyrrolo[3,4-c]carbazole-5,7(6H)-di ne; and

12-(3-Propanamide)-12,13-dihydro-5H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7(6H)-dione;

and physiologically functional derivatives thereof and solvates of any thereof for use in the manufacture of a medicament for the prophylaxis or treatment of restenosis.

3. A compound of formula (IA) wherein:



(I)

R^1 is H and R^2 is selected from:

$-OR^{6'}$, $-CO_2R^{6'}$

where $R^{6'}$ is C_{1-4}alkyl, C_{2-6}alkenyl, or H,

cyano,

$-NR^{7'}R^{8'}$

where $R^{7'}$ is H and $R^{8'}$ is C_{1-4}alkyl

$-C_{2-4}$alkyl optionally substituted with $-OR^{6'}$ where $R^{6'}$ is as defined above;

R^3 is H;

R^4 and R^5 together with the carbon atom to which they are attached form a carbonyl group (>=O);

A and B together with the carbon atoms to which they are attached each represent a phenyl ring substituted by one or more ring substituent(s) selected from:

$-OR^{6'}$, $-CO_2R^{6'}$ (where $R^{6'}$ is as defined above),

cyano,

$-C_{1-4}$alkyl optionally substituted with $-OR^{6'}$ (where $R^{6'}$ is as defined above), and

$-NR^{7''}R^{8''}$

where $R^{7''}$ and $R^{8''}$ are indepenently selected from H or C_{1-4}alkyl;

provided that when A and B are both unsubstituted phenyl rings R^2 is not ethyl or 2,3-dihydroxypropyl;

or a physiologically functional derivative thereof or a solvate of any thereof.

4. A compound of formula (IA) according to claim 3 selected from:

12-Ethyl-12,13-dihydro-10-amino-5H-indolo[2,3a]pyrrolo[3,4c]carbazole-5,7(6H)-dione;

12-Ethyl-12,13-dihydro-10-carboxy-5H-indolo[2,3a]pyrrolo[3,4c]carbazole-5,7(6H)-dione;

12-Propyl-12,13-dihydro-5H-indolo[2,3a]pyrrolo[3,4c]carbazole-5,7(6H)-dione;

12-(2,2,2-Trifluoroethyl)-12,13-dihydro-5H-indolo[2,3a]pyrrolo[3,4c] carbazole-5,7(6H)-dione;

12-(3-Hydroxypropyl)-12,13-dihydro-5H-indolo[2,3a]pyrrolo[3,4c] carbazole-5,7(6H)-dione;

12-(2,3-Dihydroxybutyl)-12,13-dihydro-5H-indolo[2,3a]pyrrolo[3,4c] carbazole-5,7(6H)-dione; and

12-(13-Acetoxypropyl)12,13-dihydro-5H-indolo[2,3a]pyrrolo[3,4c]carbazole-5,7(6H)-dione;

and physiologically functional derivatives thereof and solvates of any thereof.

5. A compound of formula (IA) as claimed in either Claim 3 or 4 for use in the treatment or prophylaxis of restenosis.

6. A method for the treatment of a mammal to prevent or alleviate restenosis, which comprises the administration of a therapeutically effective amount of a compound of formula (I) or (IA) according to any claim from 1 to 3, or physiologically functional derivative thereof or a solvate of any thereof.

7. A pharmaceutical formulation comprising of a compound of formula (IA) as defined in claim 3, or a physiologically functional derivative thereof, or a solvate of any thereof, and at least one pharmaceutical carrier or excipient and, optionally, one or more other therapeutic ingredients.

INTERNATIONAL SEARCH REPORT

Interna l Application No
PCT/GB 95/01899

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/40 C07D487/14 //(C07D487/14,209:00,209:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,93 18766 (WELLCOME) 30 September 1993 cited in the application see example 32, compound 32a ; claim 11 ---	3
A	CHEMICAL ABSTRACTS, vol. 112, no. 21, 1990 Columbus, Ohio, US; abstract no. 191499h, R. OLSEN ET AL. 'Staurosporine inhibition of intracellular free calcium transients in mitogen-stimulated Swiss 3T3 fibroblasts' page 31; see abstract & BIOCHEM. PHARMACOL. , vol. 39, no. 5, 1990 pages 968-972, --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 October 1995	- 2. 11. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Alfaro Faus, I

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INTERNATIONAL SEARCH REPORT

Intern: l Application No
PCT/GB 95/01899

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 107, no. 3, 1987 Columbus, Ohio, US; abstract no. 17329q, H. NAKANO ET AL. 'Staurosporine inhibits tyrosine-specific protein kinase activity of Rous sarcoma virus transforming protein' page 27; see abstract & J. ANTIBIOT., vol. 40, no. 5, 1987 pages 706-708, -----	1

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna. l Application No
PCT/GB 95/01899

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